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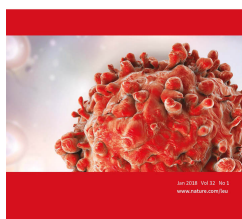
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## Leukemia



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# Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study

Reinhard Stauder, Ge Yu, Karin A. Koinig, Tim Bagguley, Pierre Fenaux, Argiris Symeonidis, Guillermo Sanz, Jaroslav Cermak, Moshe Mittelman, Eva Hellström-Lindberg, Saskia Langemeijer, Mette Skov Holm, Krzysztof Mądry, Luca Malcovati, Aurelia Tatic, Ulrich Germing, Aleksandar Savic, Corine van Marrewijk, Agnès Guerci-Bresler, Elisa Luño, Jackie Droste, Fabio Efficace, Alex Smith, David Bowen, Theo de Witte

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# Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study

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## Running Head: HRQoL in low-risk MDS

**Keywords:** HRQoL, MDS, EQ-5D, European norms, patient-reported outcome (PRO)

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46 In myelodysplastic syndromes (MDS) health-related quality of life (HRQoL) represents a relevant  
47 patient-reported outcome, which is essential in individualized therapy planning. Prospective data  
48 on HRQoL in lower-risk MDS remain rare. We assessed HRQOL by EQ-5D-questionnaire at initial  
49 diagnosis in 1690 consecutive IPSS-Low/Int-1 MDS-patients from the European LeukemiaNet  
50 Registry. Impairments were compared with age- and sex-matched EuroQol Group norms. A  
51 significant proportion of MDS-patients reported moderate/severe problems in the dimensions  
52 pain/discomfort (49.5%), mobility (41.0%), anxiety/depression (37.9%), and usual activities  
53 (36.1%). Limitations in mobility, self-care, usual activities, pain/discomfort and EQ-VAS were  
54 significantly more frequent in the old, in females, and in those with high co-morbidity burden, low  
55 haemoglobin-levels, or red blood cells transfusion-need ( $p<0.001$ ). In comparison to age- and sex-  
56 matched peers, the proportion of problems in usual activities and anxiety/depression was  
57 significantly higher in MDS-patients ( $p<0.001$ ). MDS-related restrictions in the dimension mobility  
58 were most prominent in males, and in older people ( $p<0.001$ ); in anxiety/depression in female and  
59 in younger people ( $p<0.001$ ); and in EQ-VAS in women and in persons older than 75 years  
60 ( $p<0.05$ ). Patients newly diagnosed with IPSS lower-risk MDS experience a pronounced reduction  
61 in HRQoL and a clustering of restrictions in distinct dimensions of HRQoL as compared with  
62 reference populations.

63

65 Myelodysplastic syndromes (MDS) represent challenging hematopoietic disorders characterized by  
66 cytopenias, functional blood defects and clonal hematopoiesis. The clinical course is characterized  
67 by an impaired health-related quality of life (HRQoL), the risk of transformation to acute myeloid  
68 leukaemia (AML) and reduced survival in the majority of patients.<sup>1</sup> Based on biological parameters,  
69 patients are classified into different risk groups to predict overall survival (OS) and the risk of AML  
70 transformation. The international prognostic scoring system (IPSS)<sup>2</sup> and more recently, the revised  
71 IPSS (IPSS-R)<sup>3</sup> represent the gold standard in prognostication of MDS. Based on these scoring  
72 systems, IPSS low/intermediate-1 risk and IPSS-R (very) low/intermediate risk are classified as  
73 lower-risk MDS with a low propensity to transform to AML.<sup>2,3</sup> The treatment goals in this cohort of  
74 patients are an improvement in cytopenias, prolongation of survival, and improvement and  
75 maintenance of HRQoL and functional capacities. IPSS intermediate-2/high and IPSS-R high/very  
76 high risk are classified as higher-risk MDS, which are characterized by an increased risk of AML  
77 transformation and a short median survival of less than two years.<sup>1</sup>

78  
79 Patients with MDS often suffer from a high symptom burden, resulting in restrictions in HRQoL.  
80 Assessment of HRQoL provides information on the patient's perspective and perception, thus  
81 representing a relevant patient-reported outcome (PRO).<sup>1,4,5</sup> The study of HRQoL has become an  
82 increasingly critical area of research,<sup>6</sup> as limitations in HRQoL are frequently observed in MDS and  
83 are only partially explained by anaemia.<sup>7,8</sup> Moreover, restrictions in HRQoL may predict an  
84 unfavourable clinical outcome.<sup>9-12</sup> In addition HRQoL represents a parameter of response  
85 evaluation.<sup>1,13,14</sup> Thus, the integration of assessment of HRQoL in MDS has been propagated by  
86 clinicians, stakeholders and authorities.<sup>1,13-15</sup> However, definitive data on HRQoL in low-risk MDS  
87 at initial diagnosis are limited by small sample size,<sup>16,17</sup> selection bias,<sup>7,16,17</sup> and assessment later

88 after initial diagnosis.<sup>7, 11, 16, 18, 19</sup> In addition, most studies have included patients with higher-risk  
 89 MDS,<sup>9-12, 16, 18-20</sup> AML,<sup>10, 11</sup> or CMML,<sup>11, 16</sup> which precludes precise interpretation. Lower-risk  
 90 patients with MDS are typically of advanced age with a median of 74 years at diagnosis.<sup>21</sup> The  
 91 dissection between age-associated restrictions in HRQoL and the incremental impact of MDS in  
 92 these patients is relevant, yet has not been analysed at all.

93

94 The main objective of this international prospective cohort observational study is to investigate  
 95 the HRQoL-profile of patients with lower-risk MDS at time of diagnosis, as compared with the  
 96 general population matched on age and sex. The incremental impact of MDS on symptom burden  
 97 is dissected by comparing features in MDS with the general population. A secondary objective is to  
 98 examine clinical factors associated with HRQoL of these patients.

99

## 100 **MATERIALS / METHODS**

### 101 *Participants*

102 The EUMDS Registry is a prospective, non-interventional longitudinal study, enrolling newly  
 103 diagnosed patients with IPSS low or intermediate-1 MDS from 145 haematology centres in 17  
 104 European countries and Israel. Patients with an IPSS risk intermediate-2 or high, or with therapy-  
 105 related MDS were excluded. Patients without cytogenetic information were only included if the  
 106 diagnosis of MDS was morphologically proven, with <5% bone marrow blasts and at most a single  
 107 cytopenia according to the IPSS. Based on these criteria, exclusively IPPS low or intermediate-1  
 108 patients were included in EUMDS.

109

110 Therapy is given according to local guidelines.<sup>21</sup> Enrolment was within 100 days of the diagnostic  
 111 bone marrow aspirate. The average time from date of diagnosis to inclusion was 44 days (standard  
 112 deviation 28 days). Details on design and data collection have been published elsewhere.<sup>21</sup>  
 113 As EQ-5D was not licensed in two countries, 15 countries were included in this analysis. EUMDS  
 114 (ClinicalTrials.gov: NCT00600860) has been approved by the ethics committees of all participating  
 115 centres and is performed in accordance with the Declaration of Helsinki. Written informed consent  
 116 was obtained from all patients.

### 117 *HRQoL Measurement*

118 Patient reported HRQoL was measured by the European Quality of Life five Dimensions (EQ-5D), at  
 119 the time of study enrolment. EQ-5D is a validated, generic, HRQoL-questionnaire,<sup>22</sup> consisting of  
 120 the EQ-5D descriptive system with five dimensions related to daily activities (mobility, self-care,  
 121 usual activities, pain/discomfort, anxiety/depression), with three-level answers (no problem, some  
 122 problems, severe problems), and a visual analogue scale (EQ-VAS). The five dimensions were  
 123 converted into a single summary index (EQ-5D index) by applying the European value set (EVS).<sup>23</sup>  
 124 EQ-VAS<sup>22</sup> is a global evaluation of 'own health today' using a health state scale ranging from 0  
 125 (worst imaginable) to 100 (best imaginable).

### 126 *Measures of Population Norms*

127 The main objective of this paper was to compare the QoL of patients with MDS with general  
 128 population with a similar age and gender distribution. Therefore population norms were used as  
 129 reference values to assess the relative HRQoL of patients in comparison to that of an average  
 130 person.<sup>24</sup> Population norms are based on descriptions of current health status from population  
 131 surveys. Nine European countries in this study (Denmark, France, Germany, Greece, Italy,  
 132 Netherlands, Spain, Sweden, and the UK) have reported a series of tables of age/sex population  
 133 norms for the EQ-5D for both, profile data and VAS scores.<sup>25</sup> For the five European countries and

Israel for which there are no published EQ-5D population norms, we replaced the missing data on the probabilities of being in a given level for each EQ-5D dimension with the mean of the available European countries by matching the combination of age group and gender.

### *Demographic and Clinical Parameters*

Information on patients' demographics (age and gender), IPSS-R, co-morbidity index (MDS-CI), haemoglobin (Hb)-level at the time of diagnosis, and red blood cell transfusions (RBCT) in the year prior the diagnosis were recorded.<sup>3, 21, 26</sup> Due to the small number of young adult patients, age was categorised into three groups (<60, 60–75, and 75+ years) to compare HRQoL of different age groups.

### *Statistical Analysis*

Differences in response between the five EQ-5D dimensions in patients with MDS and European norms were evaluated using chi-square tests. For both EQ-5D index and EQ-VAS, the mean score with standard deviation was calculated. Wilcoxon's signed ranks tests were conducted to identify any major difference between the MDS patient baseline values and European norms. The relationship between HRQoL and demographic/clinical factors was examined using multilevel linear regression (additional information is available in Supplementary Materials); univariate analysis was performed for age at diagnosis, gender, IPSS-R, MDS-CI, Hb and RBCT status, and a multivariate analysis was performed adjusting for all other variables. We assessed the discriminative ability of HRQoL not only by a significant difference, but also by a minimally important difference (MID).<sup>27</sup> The MID is viewed as the smallest difference in score in the domain of interest that is perceived by patients as beneficial or that would result in a change in treatment.

*See supplementary material for more detail.*

All analyses were undertaken in Stata 14 (StataCorp, College Station, TX).



## RESULTS

**Characteristics of patients**

Based on IPSS-scoring, i.e. the gold-standard in classification at the time at the start of the registry, 1985 patients were included between December 2007 and January 2016, among which 961 (48.4%) were IPSS low-risk and 912 (45.9%) were IPSS Int-1. IPSS score could not be calculated in 5.6% of patients where cytogenetic testing was not available or had failed. Based on inclusion criteria, exclusively IPSS low or int-1 patients were included. Retrospective classification by IPSS-R revealed a (very) low risk in 24.8% and 37.6%, an intermediate risk in 21.2%, high/very high risk in 6.1% and classification was unknown in 10.3% of patients. In total 1690 patients (85.1%) completed both EQ-5D descriptive system and EQ-VAS. Thirty-three patients (1.7%) completed EQ-5D description only, and 7 patients (0.3%) completed EQ-VAS only (Table 1.). The majority of patients had advanced age (median age: 74 years), and a male preponderance was observed. Nearly half of patients were characterized by Hb-levels <10g/dL at baseline, and more than 30% of patients had received RBCT within one year prior to diagnosis. Demographic characteristics of the patients who completed EQ-5D did not differ substantially from the total cohort, showing a similar age distribution and a slightly higher proportion of men. Overall, the HRQoL data in our sample were likely missing at random (Table 1).

**Patients with MDS reveal profound impairments in HRQoL**

The MDS-cohort was characterized by a mean EQ-5D index-score of 0.74 and a mean EQ-VAS of 69.6. A significant proportion of MDS-patients reported moderate or severe problems in the dimensions pain/discomfort (49.5%), mobility (41.0%), anxiety/depression (37.9%), and usual activities (36.1%), respectively. The dimension with the lowest proportion of restrictions was self-care (13.3%) (Table 2). Clinically meaningful restrictions in the dimensions mobility, self-care, usual activities, and pain/discomfort as well as in EQ-VAS and EQ-5D index were observed significantly

more often in older patients and in those with a high co-morbidity burden, low Hb-levels, or RBCT need ( $p < 0.001$ ). Increased problems with anxiety/depression were significantly more frequent in women ( $p < 0.001$ ) and in patients with lower Hb-levels ( $p < 0.01$ ). The impact both of IPSS and IPSS-R on EQ-5D scoring was only marginal. In general, restrictions in all parameters of EQ-5D were significantly more often reported in female patients ( $p < 0.05$ , Table 2).

### **Association of restrictions in HRQoL and demographic and disease factors**

To assess possible associations between clinical parameters and HRQoL, univariate and multivariate linear analyses were performed. It was estimated that patients in the reference group of each of demographic and clinical parameters would have a mean score of 0.85 on the EQ-5D index, and 80.85 on the EQ-VAS (Table 3). Relative to these scores, there was a significant loss in HRQL for groups who were older (e.g. 75+ vs <60 years; index: -0.08; VAS: -7.33), female, or had increased comorbidities, low Hb-levels or transfusion dependence (Table 3.). These differences exceeded the MID on each of the two HRQL measures ( $> 0.03$  on the EQ-5D index and  $> 3.0$  on the EQ-VAS). In summary HRQoL as defined by EQ-5D index and EQ-VAS was more often significantly impaired in older and in female patients and in persons with advanced comorbidities, low Hb-levels and increased transfusion need both in uni- and in multivariate analyses.

### **Comparison of HRQoL in MDS and in age- and sex-matched reference populations**

We compared subgroups of MDS-patients with age- and sex-matched reference norms. Overall, patients with MDS were characterized by a small, but significantly lower EQ-5D index (0.74 vs 0.76) and lower EQ-VAS (69.6 vs 71.8) than European norms ( $p < 0.05$ )(Table 4). However, these differences were too small to fulfil the criteria of MID. In contrast distinct differences which fulfilled the criteria of a MID were seen in individual components of EQ-5D: a significantly higher

proportion of MDS-patients reported moderate/severe problems in the dimensions mobility, usual activities and anxiety/depression compared to the reference populations ( $p<0.001$ )(Table 4).

Analyses stratified by sex and age depicted most pronounced differences in the dimensions anxiety/depression, and usual activities, in all age groups, and in both sexes ( $p<0.001$ ). Compared to peers, prevalence of problems in anxiety/depression was most prominent in female (16.7 vs. 50.3%; Fig. 1B), and in younger patients (9.8 vs. 40.8%,  $p<0.001$ ; Fig. 2A). Restrictions in mobility were most pronounced in male (Fig. 1A), and in older patients (60+ years;  $p<0.01$ ; Fig. 2C). The dimensions self-care and pain/discomfort were not different between the cohorts (Table 2; Figure 1 & 2). Differences in EQ-5D index were most pronounced in younger MDS-patients (<60yrs). EQ-VAS was more often diminished at advanced age (75+ yrs) as compared to peers ( $p<0.001$ ; Table 2). These differences fulfilled the criteria of a MID.

## DISCUSSION

This prospective cohort observational study adds substantial information on the prevalence and clustering of restrictions in HRQoL in lower-risk Patients with MDS at diagnosis. In a cross-sectional analysis, we observed profound restrictions in distinct dimensions of the EQ-5D when compared with European reference populations. Moreover, we identified demographic and clinical factors, which are associated with restrictions in HRQoL.

### Prevalence of restrictions in HRQoL in MDS at initial diagnosis / Factors associated with decreased HRQoL

Data on symptom burden in lower-risk MDS at initial presentation are rare, and limited by small sample size,<sup>16, 17</sup> selection bias,<sup>7, 16, 17</sup> and analyses performed later after initial diagnosis.<sup>7, 11, 16, 18,</sup>

228 <sup>19</sup> In addition, most studies have included patients with higher risk MDS,<sup>9-11 9-11, 16, 18-20</sup>, AML<sup>10, 11</sup> or  
 229 CMML<sup>11, 16</sup>, which precludes precise interpretation. The strength of our study is the large number  
 230 of observations at initial diagnosis and the parallel analysis of the different parameters of the  
 231 validated score EQ-5D including EQ-5D VAS, EQ-5D index as well as the different EQ-5D  
 232 dimensions in a homogenous cohort of lower-risk patients. This is the first report to present  
 233 details on restrictions in the distinct domains of EQ-5D in MDS, which reveals huge differences in  
 234 HRQoL-profile in daily activities. These findings are particularly relevant, as studies from the  
 235 literature reported exclusively EQ-5D summary scores and EQ-5D VAS,<sup>16, 20</sup> but lacked a  
 236 presentation of EQ-5D daily activities.

237  
 238 Our study shows a pronounced symptom burden in many patients with MDS, predominantly in the  
 239 dimensions pain/discomfort, mobility, anxiety/depression, and usual activities. Moreover, a  
 240 clustering of symptoms in distinct subgroups of patients is revealed. The low percentage of self-  
 241 reported problems in the dimension self-care, particularly in elderly is remarkable. This  
 242 phenomenon has been observed across different cancer types<sup>28</sup> and may be explained by focusing  
 243 on “washing and dressing” in the definition of self-care, whereas functional capacities like “work,  
 244 housework, family or leisure activities” are assessed in the dimension “usual activities”.

245  
 246 We demonstrated that advanced age, pronounced co-morbidities, low Hb-levels, RBCT need, and  
 247 female sex, were significantly associated both with a decreased EQ-5D index, and decreased EQ-  
 248 VAS after adjustment for co-variables. These observations extend data from the literature<sup>7, 8, 18, 20</sup>  
 249 and define cohorts of patients which are at high risk of decreased HRQoL. Hb-levels<sup>7, 18, 20</sup> and  
 250 transfusion dependence<sup>20</sup> are important predictors of HRQoL, both in this study and in the  
 251 literature. Effective treatment for anemia and reduction of transfusion need might thus contribute

to improvement and maintenance of HRQoL.<sup>17</sup> Future studies will focus on the prediction of deterioration of HRQoL, and focus on early prevention.

A relevant aspect of our work is the significant difference in symptom burden in patients with MDS as compared to age- and sex matched European reference populations. Thus, dissection of features which are MDS-specific from symptoms which are present in matched general populations is possible. This study reveals an incremental symptom burden in MDS characterized by pronounced age- and sex-dependent differences in the distinct EQ-5D dimensions. Both young and old patients suffer from troublesome MDS-related symptoms. Data from the literature are rare and have been characterized by a small sample size and were restricted to one country.<sup>16, 17</sup> The study of Hellstrom evaluated HRQoL at later time points after diagnosis, and was focused on selecting anaemic patients with a high probability for response to ESAs for a clinical study.<sup>17</sup> The study of Jansen<sup>16</sup> reported exclusively EQ-5D VAS but lacked a presentation of EQ-5D daily activities for which we show strong differences. Moreover, patients in Jansen's study were entered at variable time points after diagnosis, and included patients with higher risk MDS and CMML.<sup>16</sup>

The high prevalence of anxiety/depression and of limitations in usual activities is more pronounced in women in our study. These observations form the basis to appreciate the relevance of MDS on individual health in a given patient and the opportunity to assist health care providers in managing the relevant symptoms.<sup>8</sup> Thus, patient-centred care will be improved by special attention to patient subgroups.<sup>29, 30</sup> The finding of the difference of depression between our MDS patients and the general population is corroborated by similar evidence in other hematologic conditions. For example, Efficace et al.<sup>31</sup> observed that depression was one of the most impaired psychological domains in a sample of chronic myeloid leukemia patients as compared to their

peers in the general population; and, similar to our findings, this impairment was most pronounced in female patients. In agreement with other studies,<sup>8, 32, 33</sup> differences by gender were observed with lower HRQoL being more pronounced in females. Although the discussion of causes of disparity in gender-based distribution is beyond the scope of this manuscript, gender-specific evaluations and interventions should be discussed or suggested in patients with MDS.

The relevance of anxiety/depression in patients with MDS is supported by the fact that 9.5% of EU-MDS patients receive antidepressants at baseline,<sup>21</sup> and that impairments in depression screening by geriatric depression scale (GDS) are observed in 24% of patients with MDS<sup>34</sup>. Likewise “emotional health” and “uncertainty/sense of control” have been highly ranked by patients and caregivers in a recent study.<sup>35</sup> To address the individual needs of patients with MDS, the novel, disease specific score for MDS, QUALMS,<sup>18, 35</sup> is currently applied and validated in the EUMDS-cohort. Our study also confirms that age- and sex-dependent baseline values in HRQoL should be considered when interpreting the results of clinical studies in MDS that use HRQoL as an endpoint, as suggested recently.<sup>4, 8</sup>

**Strengths** of this work are the large number of observations, the well-defined inclusion criteria in a non-interventional registry, the enclosure of newly diagnosed MDS-patients within 100 days of the date of the diagnostic bone marrow aspirate, and the parallel analysis of the different parameters of the validated generic score EQ-5D.<sup>21</sup> Based on the use of a generic questionnaire, comparisons with reference populations are possible.

**Limitations:** Disease-specific scores may more accurately reflect the spectrum in a given disease. To address this aspect, the MDS-specific score QUALMS has been developed recently.<sup>18, 35</sup> QUALMS has been integrated in EUMDS in a recently amended version of the protocol. Based on objectives of this study and the EUMDS-registry, analyses have been restricted to IPSS lower-risk

MDS. Therefore, this study does not allow conclusions on MDS in general. However, the recently introduced new protocol of the registry will register all subtypes of MDS. Other aspects of HRQoL, which might be relevant for the outcome of patients e.g. the deterioration of HRQoL over time, have not yet been analysed. These investigations are currently performed in several studies focusing on the impact of specific interventions on HRQoL.

### **In summary**

This is the first study to analyse prospectively the patient reported outcome HRQoL in IPSS lower-risk MDS at diagnosis, and to compare patients with MDS with age- and sex matched healthy populations. Patients experience profound age- and sex-dependent restrictions in different HRQoL-dimensions. Distinct demographic and disease parameters are associated with reduced HRQoL. These observations should form the basis for individualized treatment directed at relief of distinct symptoms. In addition, these results may provide a benchmark in the evaluation of new interventional options aimed at improving HRQoL outcomes.

**Supplementary information** is available at Leukemia ([www.nature.com/leu](http://www.nature.com/leu)) providing additional information regarding (i) EQ-5D index and EVS; (ii) on the comparison of patients with MDS and the reference population; (iii) on multivariate analysis; and (iiii) on minimally important difference (MID)

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### Authorship Contributions

Explanation of author contributions: Conception and design: TdW, DB, SL, ASi, RS, JC, PF, UG, MSH, AG, LM, KM, ASa, GS, EH, CvM; Collection and assembly of data: all co-authors; Data analysis and/or interpretation: RS, KK, CvM, GY, AS, TDW; Manuscript writing: all co-authors; Final approval of manuscript: all co-authors

### Disclosure of Conflicts of Interest

Conflict of interest disclosure: This study was carried out within the EUMDS Registry which is supported by Novartis Oncology. T. de Witte is the project leader and C. van Marrewijk is the project manager of the EUMDS Registry. The authors declare no competing financial interests in relation to this work. Outside the funding by Novartis Oncology, the following co-authors report grants or personal fees: R.Stauder received research funding and honoraria from Celgene, Teva and Novartis. T. de Witte reports grants from Celgene, personal fees from Incyte, personal fees from Amgen, personal fees from Incyte outside the submitted work. G. Sanz reports personal fees by Celgene. M. Mittelman reports personal fees by Ofizer, Amgen, research grants by Celgene / Neopharm, and advisory roles for Celgene, Amgen, and Janssen. A. Savic personal fees by Seattle Genetics, Novo Nordisk, and Amgen. F. Efficace reports personal fees by Bristol-Myers Squibb, Seattle Genetics, TEVA and Incyte; and research funding by Lundbeck, TEVA and Amgen.



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**Fig 1: Proportion of moderate/severe problems in male (A) and female (B) patients with MDS (blue bars) as compared to European age- and sex matched standard population (dark grey). Standard errors indicated as lines. Differences ( $\Delta$ ) of patients with MDS to sex-matched reference group shown when significant (\*\*\*)  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ ; as assessed by Wilcoxon signed rank tests).**

**Fig 2: Proportion of moderate/severe problems by age group (<60 (A), 60-75 (B) or >75 (C) years old) in patients with MDS (blue bars) as compared to European age- and sex matched standard population (dark grey). Standard errors indicated as lines. Differences ( $\Delta$ ) of patients with MDS to sex-matched reference group shown when significant (\*\*\*)  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ ; as assessed by Wilcoxon signed rank tests).**

**Table 1. Demographic and clinical characteristics of MDS-patients - entire cohort and EQ-5D respondents**

Characteristic	Total		EQ-5D Completed ♦		EQ-5D Not completed	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Entire Cohort	1 985	100.0	1 690	85.1	295	14.9
Age, years						
<60	214	10.8	187	11.1	27	9.2
60-75	818	41.2	707	41.8	111	37.6
75+	953	48.0	796	47.1	157	53.2
Gender						
Male	1 202	60.6	1 039	61.5	163	55.3
Female	783	39.4	651	38.5	132	44.7
Diagnosis (WHO 2001)						
RA	355	17.9	283	16.7	72	24.4
RARS	310	15.6	276	16.3	34	11.5
RCMD	755	38.0	651	38.5	104	35.3
RCMD-RS	118	5.9	102	6.0	16	5.4
RAEB-1	239	12.0	207	12.2	32	10.8
RAEB-2	9	0.5	8	0.5	1	0.3
MDS-U	81	4.1	68	4.0	13	4.4
5q-Syndrome	118	5.9	95	5.6	23	7.8
IPSS						
Low risk	961	48.4	813	48.1	148	50.3
Intermediate-1	912	45.9	782	46.3	130	43.9
Low/int-1 no cytogenetics*	112	5.6	95	5.6	17	5.7
IPSS-R						
Very low risk	493	24.8	433	25.6	60	20.3
Low risk	746	37.6	646	38.2	100	33.9
Intermediate risk	420	21.2	341	20.2	79	26.8
High/very high risk	121	6.1	110	6.5	11	3.7
Unknown	205	10.3	160	9.5	45	15.3
MDS-CI						
Low risk	1 276	64.3	1 076	63.7	200	67.8
Intermediate risk	606	30.5	525	31.1	81	27.5
High risk	103	5.2	89	5.3	14	4.7
Hemoglobin (g/dL)						
≥10	1 076	54.2	913	54.0	163	55.3
<10	884	44.5	768	45.4	116	39.3
Unknown	25	1.3	9	0.5	16	5.4
Red Blood Cell Transfusion #						
No	1 390	70.0	1 163	68.8	227	76.9
Yes	595	30.0	527	31.2	68	23.1

Abbreviations: WHO, World Health Organization; IPSS International Prognostic Scoring System, IPSS-R, Revised International Prognostic Scoring System; MDS-CI, Myelodysplastic Syndrome-Comorbidity Index; HCT-CI, Hematopoietic Cell Transplant-Comorbidity Index.

◆ Includes EQ-5D completed only, EQ VAS completed only and both completed.

\* Patients with cytogenetics failed or not available were included if the diagnosis of MDS was morphologically proven, with <5% bone marrow blasts and at most a single cytopenia according to the IPSS. Based on these criteria exclusively IPPS low or int-1 patients were included in this cohort.

# as assessed in the year prior to initial diagnosis

Accepted manuscript

Mobility		Self-care		Usual Activities		Pain/Discomfort		Anxiety/Depression		mean
Problem <sup>a</sup>		Problem <sup>a</sup>		Problem <sup>a</sup>		Problem <sup>a</sup>		Problem <sup>a</sup>		
%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	

Total	41.0	13.3	36.1	49.5	37.9	0.74
Sex	0.007	0.030	0.021	<0.001	<0.001	
Male	39.1	11.6	33.6	45.5	30.1	0.77
Female	44.0	16.0	40.0	55.9	50.3	0.69
Age Group (years)	<0.001	<0.001	<0.001	<0.001	0.581	
<60	18.5	2.7	26.6	31.5	40.8	0.80
60-75	33.0	8.5	29.1	43.5	35.9	0.78
75+	53.3	20.0	44.5	58.9	39.0	0.69
IPSS	0.083	0.057	0.899	0.005	0.884	
Low risk	42.4	13.2	49.6	53.1	39.2	0.74
Intermediate risk	38.2	13.1	47.7	49.3	36.8	0.75
Low/int-1 no cytogenetics*	51.6	16.1	64.5	44.7	36.6	0.70
IPSS-R	0.656	0.907	0.899	0.023	0.119	
Very low risk	40.6	11.9	32.4	53.1	33.8	0.75
Low risk	40.8	13.0	36.6	49.3	38.9	0.73
Intermediate risk	42.4	14.4	36.5	44.7	42.9	0.73
High/very high risk	40.4	14.7	35.8	52.3	36.7	0.76
Unknown	40.6	15.0	43.1	48.8	35.0	0.74
MDS-CI	<0.001	<0.001	<0.001	<0.001	0.493	
Low risk	33.9	10.1	31.6	44.5	37.3	0.76
Intermediate risk	51.8	18.4	42.8	57.2	38.4	0.70
High risk	63.6	22.7	50.0	64.8	42.0	0.67
Haemoglobin (g/dL)	<0.001	<0.001	<0.001	0.026	0.002	
>=10	34.5	9.2	28.9	46.9	34.3	0.77
<10	49.2	18.3	45.0	53.2	42.4	0.70
Unknown	0.0	0.0	0.0	0.0	22.2	0.95
Red Blood Cell Transfusion #	<0.001	<0.001	<0.001	0.049	0.070	
No	35.9	9.8	30.9	47.5	36.2	0.76
Yes	52.2	21.0	47.4	53.9	41.7	0.69

\* Patients with cytogenetics failed or not available were included if the diagnosis of MDS was morphologically proven, with <5% bone marrow blasts and at most a exclusively IPPS low or int-1 patients were included in EUMDS.

**Table 3. Association of HRQL and demographic and disease characteristics in MDS-patients based on univariate and multivariate analyses**

Table 3: Association of Hb, age, demographic and disease characteristics in MDS patients based on univariate and multivariate analysis										
Variable	EQ-5D Index (n = 1,681 patients)									
	Univariate				Multivariate *					
	coef.	95% CI		p	coef.	95% CI		p	coef.	95% CI
Constant	0.74	0.73	0.76	<0.001	0.85	0.81	0.89	<0.001	70.71	67.98
Age Group										
<60										
60-75	-0.03	-0.06	0.01	0.144	-0.02	-0.05	0.02	0.287	-3.12	-6.23
75+	-0.11	-0.14	-0.07	<0.001	-0.08	-0.12	-0.05	<0.001	-10.06	-13.19
Sex										
Male										
Female	-0.07	-0.09	-0.05	<0.001	-0.08	-0.10	-0.06	<0.001	-3.24	-5.17
IPSS-R										
Very low risk										
Low risk	-0.01	-0.04	0.02	0.414	0.03	0.00	0.06	0.045	-2.19	-4.59
Intermediate/high risk	-0.01	-0.04	0.03	0.750	0.04	0.01	0.07	0.022	-2.68	-5.42
Unknown	0.00	-0.04	0.04	0.909	0.02	-0.02	0.07	0.254	-0.01	-3.69
MDS-CI										
Low risk										
Intermediate/high risk	-0.07	-0.09	-0.04	<0.001	-0.06	-0.08	-0.04	<0.001	-7.33	-9.26
Hemoglobin (g/dL)										
>=10										
<10	-0.07	-0.09	-0.04	<0.001	-0.05	-0.08	-0.03	<0.001	-7.12	-8.99
Red Blood Cell Transfusion #										
No										
Yes	-0.07	-0.10	-0.05	<0.001	-0.04	-0.07	-0.02	<0.001	-7.14	-9.14
Abbreviations: IPSS-R, Revised International Prognostic Scoring System; MDS-CI, Myelodysplastic Syndrome-Comorbidity Index. # as assessed in the year prior to initial diagnosis: * adjusted for all other variables										

Abbreviations: IPSS-R, Revised International Prognostic Scoring System; MDS-CI, Myelodysplastic Syndrome-Comorbidity Index.  
# as assessed in the year prior to initial diagnosis; \* adjusted for all other variables



**Table 4. Comparison of HRQL in MDS-patients and age and sex matched European ref**

Table 1: Comparison of HRQL in MDS patients and age- and sex-matched European Norm											
	Mobility		Self-care		Usual Activities		Pain/Discomfort		Anxiety/Depression		EQ
	Problem*		Problem*		Problem*		Problem*		Problem*		mean
	%	p	%	p	%	p	%	p	%	p	
Entire Cohort	<0.001		0.438		<0.001		0.919		<0.001		
European Norm	33.5		12.4		26.0		48.8		14.9		0.76
EUMDS	41.0		13.3		36.1		49.5		37.9		0.74
Male	<0.001		0.409		<0.001		0.371		<0.001		
European Norm	29.4		10.7		23.4		43.9		13.7		0.79
EUMDS	39.1		11.6		33.6		45.5		30.1		0.77
Female	0.142		0.820		<0.001		0.355		<0.001		
European Norm	40.0		15.0		30.1		56.8		16.7		0.72
EUMDS	44.0		16.0		40.0		55.9		50.3		0.69
Age Group, <60	0.202		0.288		<0.001		0.645		<0.001		
European Norm	13.6		4.9		11.4		28.3		9.8		0.86
EUMDS	18.5		2.7		26.6		31.5		40.8		0.80
Age Group, 60-75	0.002		0.179		<0.001		0.606		<0.001		
European Norm	25.4		6.7		20.0		44.5		14.9		0.79
EUMDS	33.0		8.5		29.1		43.5		35.9		0.78
Age Group, 75+	<0.001		0.711		<0.001		0.671		<0.001		
European Norm	45.2		19.1		34.6		57.4		16.0		0.71
EUMDS	53.3		20.0		44.5		58.9		39.0		0.69
◆ Problem: moderate or severe problems											

♦ Problem: moderate or severe problems

Figure 1

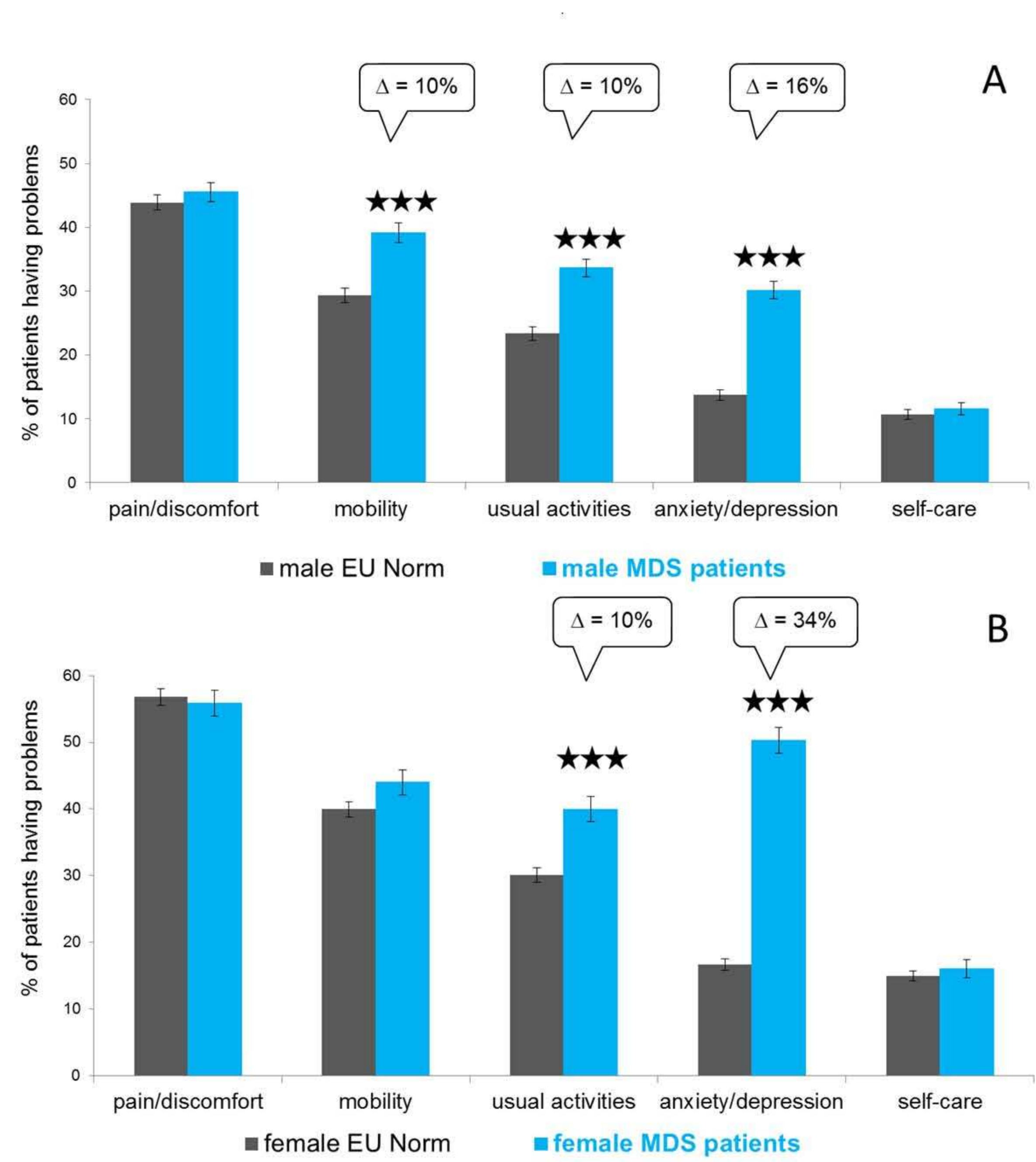


Figure 2

